REMARKS

The Present Invention

The present invention is directed to an adenoviral vector comprising an adenovirus serotype 5 genome and comprising a nucleic acid sequence encoding pigment epithelium-derived factor (PEDF) or a therapeutic fragment thereof, wherein the nucleic acid sequence is operably linked to a CMV promoter, the adenoviral vector is rendered replication deficient by deletion of all of the E1 region and all of the E4 region, and the adenoviral vector comprises a pGUS spacer sequence in the E4 region.

The Pending Claims

Claims 1, 8, 11-14, and 18-27 are pending. All of the pending claims are directed to the adenoviral vector described above.

The Amendments to the Specification

The specification has been amended to include text from U.S. Patent 5,851,806 (Kovesdi et al.) ("the '806 patent") (see '806 patent specification at col. 8, line 45 – col. 9, line 52). The disclosure of the '806 patent has been incorporated by reference into the present application (see specification at page 6, lines 12-15, and page 7, lines 2-4). As such, the amendment to the specification adds no new matter to the present application (see M.P.E.P. § 2163.07(b)).

The Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the present invention. Claims 1 and 39 have been amended to incorporate the subject matter of cancelled claims 4, 6, 38, 40, 41, and 44, and a portion of the subject matter of cancelled claim 15. Claims 1 and 39 also have been amended to recite that the adenoviral vector (i) comprises an adenovirus serotype 5 genome, (ii) is rendered replication deficient by deletion of all of the E1 region and all of the E4 region (i.e., there are no other deletions of replication-essential gene functions), and (iii) comprises a pGUS spacer in the E4 region, wherein the pGUS spacer sequence comprises an SV40 polyadenylation sequence. These amendments are supported by the specification at, for example, page 5, lines 16-18, page 6, line 3, page 6, line 16 – page 17, line 15, and by the text of U.S. Patent 5,851,806 that has been included in the present application by way of the specification amendments discussed above. Also discussed above, the '806 patent has been incorporated by reference into the present

application. Claims 4-6, 9, 15-17, and 38-44 have been cancelled. Accordingly, no new matter has been added by way of these claim amendments.

The Office Action

The Office Action has made the restriction requirement of May 20, 2003, final, and has withdrawn claims 9, 16, 17, 22, and 23 from further consideration as being drawn to a nonelected species. Claims 1, 4-6, 8, 11, 15, 21, 24-27, 38-41, and 43-44 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent 6,288,024 (Bouck et al.) in view of U.S. Patent 5,827,702 (Cuthbertson) and U.S. Patent 6,228,646 (Hardy). The Office Action rejects claims 1, 4-6, 8, 11-12, 15, 21, 24-27, 38-41, and 43-44 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of the disclosures of the Bouck '024 patent, the Cuthbertson '702 patent, and the Hardy '646 patent in further view of U.S. Patent 5,962,311 (Wickham et al.), but refers to a reference by Palmiter et al. rather than the Wickham '311 patent. The Office Action also rejects claims 1, 4-6, 8, 11, 15, 18-21, 24-27, 38-41, and 43-44 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of the disclosures of the Bouck '024 patent, the Cuthbertson '702 patent, and the Hardy '646 patent in further view of U.S. Patent 5,962,311 (Wickham et al.). Reconsideration of these rejection is hereby requested.

Discussion of Rejections under 35 U.S.C. § 103(a)

The Office Action has rejected claims 1, 4-6, 8, 11, 12, 15, 18-21, 24-27, 38-41, and 43-44 under Section 103 as allegedly encompassing obvious subject matter in view of the Bouck '024 patent , the Cuthbertson '702 patent, and the Hardy '646 patent, by themselves or in further view of the disclosure of an unnamed Palmiter reference or the disclosure of the Wickham '311 patent reference. Claims 4-6, 15-17, 38-44 have been cancelled. These rejections are respectfully traversed for the reasons set forth below.

To establish a *prima facie* case of obviousness under Section 103 based on a combination of references, (i) the references must disclose or suggest every element of the claimed invention, (ii) there must be a motivation to combine the references, and (iii) the combination of references must provide a reasonable expectation of success for making the claimed invention. M.P.E.P. § 2143.

The Office Action contends that the Bouck '024 patent discloses the use of adenoviral vectors encoding SLED, alone or in combination with other anti-angiogenic factors, to inhibit angiogenesis within a tissue, such as eye tissue. The Bouck '024 patent also allegedly discloses the use of a CMV promoter to regulate expression of SLED. The Office Action

concedes that the Bouck '024 patent does not disclose a replication deficient adenoviral vector lacking all of the E1 and E4 regions encoding PEDF or a therapeutic fragment thereof, nor does it disclose using an adenoviral vector encoding SLED to treat eye disease.

The Cuthbertson '702 patent allegedly discloses a method for generating a genetically engineered *in situ* ocular cell using an adenoviral vector encoding a protein useful in the treatment of ocular disease. The Office Action contends that the Hardy '646 patent discloses adenoviral vectors containing deletions of all of the early and late regions (a "gutless" vector) which can encode a gene of interest operably linked to a CMV promoter. The deletion of all of the adenoviral gene regions reportedly results in a reduced host immune response.

The Office Action contends that it would have been obvious to one of ordinary skill in the art to use an adenoviral vector encoding SLED (as allegedly taught by the Bouck '024 patent) to inhibit angiogenesis associated with eye disorders, because the Cuthbertson '702 patent allegedly discloses treatment of ocular disease using an adenoviral vector encoding a protein of interest. The Office Action further contends that one of ordinary skill in the art would be motivated by the disclosure of the Hardy '646 patent to modify the adenoviral vector disclosed in the Bouck'024 patent and use an adenoviral vector lacking all of the coding regions of the adenoviral genome, thereby arriving at the claimed invention. Moreover, the Office Action contends that one of ordinary skill in the art would be motivated by the disclosure of the Wickham '311 patent, which allegedly discloses a recombinant adenovirus comprising a chimeric fiber protein, to modify the adenoviral vector disclosed in the Hardy '646 patent and the Bouck '024 patent and use an adenoviral vector comprising a chimeric coat protein as described in claims 18-20.

Applicants note that the "Palmiter et al." reference is mentioned in the Office Action, but is not identified by citation or patent number, which prevents applicants from further discussing this reference.

The pending claims, as amended, recite a rather specific replication deficient adenoviral vector. The adenoviral vector comprises a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof, wherein (a) the nucleic acid sequence is operably linked to a CMV promoter, (b) the adenoviral vector is rendered replication deficient by deletion of all of the E1 region and all of the E4 region (and not by other deletions), and (c) the adenoviral vector comprises a pGUS spacer sequence in the E4 region, with the pGUS spacer sequence comprising an SV40 polyadenylation sequence. Thus, the pending claims do not encompass an adenoviral vector lacking all of the coding regions of the adenoviral genome (a gutless vector) in accordance with the cited references as interpreted in the Office Action. The cited references do not disclose or suggest an adenoviral vector encoding PEDF, which is rendered replication

deficient by deletion of all of the E1 region and all of the E4 region, as recited in the pending claims, let alone such an adenoviral vector that comprises a spacer sequence located in the deleted E4 region, especially a pGUS spacer sequence comprising an SV40 polyadenylation sequence. Simply put, the cited references do not disclose or suggest all of elements of the pending claims.

Moreover, even assuming arguendo that the cited references disclose or suggest all of the elements of the pending claims, one of ordinary skill in the art would not have been motivated to employ an adenovirus to deliver a therapeutic transgene to the eye, and would not have reasonably believed that such an approach would be successful. At about the time of filing of the patent application to which the present application claims priority, the scientific literature acknowledged that untoward immune responses against adenoviral vector limited the utility of adenoviral vector in the eye. For example, Reichel et al. (*Gene Therapy*, *5*, 1038-1046 (1998), provided herewith) concluded that immune responses against an adenovirus vector limited the utility of adenoviral vectors in the eye. In addition, Shen et al. (*Arch. Ophthalmol.*, *119*, 1033-1043 (2001), provided herewith) reports that adenoviral-mediated transgene expression is toxic to the retina, an adverse event that could not be abrogated by immunosuppressants. Thus, under the circumstances, the invention defined by the pending claims is unobvious in view of the cited references, whether considered alone or in combination, even if the cited references are considered to disclose or suggest all of the elements of the pending claims.

Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness, or, if established, such a *prima facie* case of obviousness is rebutted. The Section 103 rejections should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

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